REMARKS

Amendment

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Incorporation by reference of essential material

The Examiner cited improper incorporation of essential material. Applicants submit that the specification describes a method of constructing the disclosed mutants by conjugal mating followed by sequential selection in selection media. A description of donor plasmids pKO500 and pKO505, and the method of making the mutants by mobilization of donor plasmids by conjugal mating followed by sequential selection is found in Example 4, referenced in Dworkin, et al., (1996) *Mol. Microbiol.* 19:1241-1253 and Blaser, et al., (1985) *J. Infect. Dis.* 151:227-235. Applicants submit that a person having ordinary skill in this art would be able to construct the claimed mutants given the teachings of the instant specification

in view of the references which incorporate non-essential subject matter. The Examiner has not provided a detailed legal and scientific argument underlying a conclusion that a person having ordinary skill in this art would not have been enabled to create the claimed mutants given the teachings of Applicant's specification. Accordingly, Applicants respectfully request that this objection to the specification be withdrawn.

The 35 U.S.C. §112 Rejection

Claims 10-17 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

The Examiner required deposit of a mutant strain that contains a mutated recA gene before the claims will be allowed. Applicants submit that document showing deposit of a mutant strain that contains a mutated recA gene will be furnished to the Examiner as soon as the document is received by the Applicants. Accordingly, Applicants respectfully request that the rejection of claims 10-17 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 8 and 14 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The rejection is traversed.

Claim 8 recites a Markush group containing an antigen and a therapeutic agent. In the Office Action mailed April 27, 2000, the Examiner argued that claim 1 from which claim 8 depends recites that the protein is an antigen already. Additionally, in the Office Action mailed November 22, 2000, the Examiner again argued that claim 1 recite the word antigen.

However, as amended in the response filed August 3, 2000, claim 1 reads as follows: "A non-naturally occurring mutant *C. fetus* strain useful for vaccinating an animal to *Campylobacter fetus*, wherein said strain is mutated to contain a DNA cassette encoding a heterologous protein." Hence, claim 1 does not recite an antigen. Claim 1 as amended in the present response also does not recite an antigen. Applicants submit that claim 8 further limits the heterologous protein in claim 1 to an antigen or a therapeutic agent, and the subject matter which the applicants regard as the invention has been particularly pointed out and distinctly claimed. Claim 14 has been cancelled. Accordingly, Applicants respectfully request

that the rejection of claims 8 and 14 under 35 U.S.C. §112, second paragraph, be withdrawn.

The 35 U.S.C. §102 Rejection

Claims 1-2, 6-8 were rejected under 35 U.S.C. §102(a) as being anticipated by **Dworkin** et al (March 1996). The rejection is respectfully traversed.

Dworkin et al. disclosed that wild type strains of *Campylobacter fetus* vary the antigenicity of the surface layer proteins (SLPs) by reciprocal recombination events among the eight genomic SLP gene cassettes. In contrast, claim 1 is drawn to a mutant strain of *Campylobacter fetus* that contains a DNA cassette encoding a heterologous protein, wherein the insertion of said DNA cassette results in alteration of a *sapA* homolog, and the expression of said DNA cassette results in a S-layer protein that represents a chimera between the native S-layer protein and the heterologous protein encoded by said DNA cassette. **Dworkin** et al. did not teach or suggest insertion of a DNA cassette encoding a foreign heterologous protein alters a *sapA* homolog, nor did **Dworkin** et al.

teach or suggest the expression of said DNA cassette results in a chimera between the native S-layer protein and the heterologous protein encoded by said DNA cassette. Hence, the claims in the instant invention are different and distinct from that of **Dworkin** et al.

Claim 6 is drawn to a mutant strain of *Campylobacter fetus* that contains a DNA cassette containing a heterologous protein inserted between a 5' binding region and a 3' secretion signal region. Claim 7 is drawn to a strain of *Campylobacter fetus* that contains a DNA cassette with a 3' secretion signal region but no 5' binding region. **Dworkin** et al. did not teach or suggest a DNA cassette encoding a heterologous protein flanked by a 3' secretion signal region with or without a 5' binding region. In the Office Action mailed April 27, 2000, the Examiner argued that "inherently the strains would evidence a 5' binding region and 3' secretion signal region with rearranged sequences between". However, **Dworkin** et al. only taught recombination events among the eight genomic SLP gene cassettes; therefore, **Dworkin** et al. only taught genomic homologous sequences flanked by a 5' binding region and

a 3' secretion signal region. **Dworkin** et al. did not teach or suggest heterologous protein sequence flanked by a 5' binding region and a 3' secretion signal region as claimed herein. Hence, the claims in the instant invention are different and distinct from that of **Dworkin** et al.

Claim 8 is drawn to a mutant *Campylobacter fetus* strain of claim 1 that expresses a heterologous protein such as an antigen or a therapeutic agent. **Dworkin** et al. did not teach or suggest a mutant strain that expresses foreign heterologous protein as claimed herein. Since **Dworkin** et al. does not teach or suggest each and every aspect of the present invention, **Dworkin** et al. does not anticipate the present invention. Accordingly, Applicants respectfully request that the rejection of claims 1-2, 6-8 under 35 U.S.C. §102(a) be withdrawn.

Claims 14 and 16 were rejected under 35 U.S.C. §102(b) as being anticipated by **Dworkin** et al. (June 1995). The rejection is respectfully traversed.

Dworkin et al. teach the cloning of *sapB* gene in *Campylobacter fetus*. In contrast, claim 16 is drawn to a non-

Campylobacter fetus bacteria strain modified to express the *sapCDEF* gene. **Dworkin** et al. did not teach or suggest a non-*Campylobacter fetus* bacteria strain modified to express the *sapCDEF* gene. The present invention is distinct and different from that of **Dworkin** et al. Since **Dworkin** et al. does not teach or suggest each and every aspect of the present invention, **Dworkin** et al. does not anticipate the present invention. Claim 14 has been cancelled. Accordingly, Applicants respectfully request that the rejection of claims 14 and 16 under 35 U.S.C. §102(b) be withdrawn.

Claims 1-2, 4, 6-8 were rejected under 35 U.S.C. §102(b) as being anticipated by **Blaser** (November 1994 or November 1993). The rejection is respectfully traversed.

Blaser (November 1993) taught rearrangement of several genes encoding S-layer proteins results in antigenic variation in *Campylobacter fetus.* However, **Blaser** did not teach or suggest insertion of a DNA cassette encoding a foreign heterologous protein alters a *sapA* homolog, nor did **Blaser** teach or suggest the expression of said DNA cassette results in a chimera between the

native S-layer protein and the heterologous protein encoded by said DNA cassette. Hence, the claims in the instant invention are different and distinct from that of **Blaser**. Since **Blaser** (November 1993) does not teach or suggest each and every aspect of the present invention, **Blaser** (November 1993) does not anticipate the present invention.

In the abstract of **Blaser** et al. (November 1994), it is disclosed that "disruption of sapA by a gene targeting method (insertion of kanamycin resistance) caused the loss of *C. fetus* cells bearing full-length S-layer proteins and their replacement by cells bearing a 50 kDa truncated protein that was not exported to the cell surface" (lines 5-9). In contrast, the present invention is drawn to expression of a DNA cassette encoding a foreign heterologous protein results in surface expression of a chimera of the native S-layer protein and said heterologous protein in *C. fetus*. Hence, the claims in the instant invention are different and distinct from that of **Blaser** et al. Since **Blaser** (November 1994 or November 1993) does not teach or suggest each and every aspect of the present invention, **Blaser** (November 1994 or November 1993) does not anticipate the present invention. Accordingly, Applicants request

that the rejection of claims 1-2, 4, 6-8 under 35 U.S.C. §102(b) be withdrawn.

The 35 U.S.C. §103(a) Rejection

Claims 1-2, 4-9 were rejected under 35 U.S.C. §103(a) as being unpatentable over **Blaser** (1994) in view of **Lubitz** et al. The rejection is respectfully traversed.

As discussed above, **Blaser** et al. (1994) teaches away from the present invention in that **Blaser** (1994) disclosed the insertion of a kanamycin cassette into sapA results in a truncated protein that was not exported to the cell surface. In contrast, the instant invention is drawn to expression of a chimeric S-layer protein, i.e. the chimera is expressed on the surface of the bacteria.

The Examiner argued that "**Blaser** clearly teaches the use of *C. fetus* as a strain that is useful for the evaluation of the immune system of a mammalian host and in evaluating the immune response to antigens expressed (immunoblot)." Applicants respectfully disagree.

Blaser did not teach or suggest using *C. fetus* for the evaluation of the immune system of a mammalian host or in evaluating the immune response to antigens expressed. **Blaser** used immunoblot to determine the size of full-length S-layer proteins expressed in mutant *C. fetus* strains after incubating the bacteria with serum (lines 9-12). The immunoblot did not measure any immune response to *C. fetus* in a host. **Blaser** disclosed the antigenic and virulence characteristics of the mutant *C. fetus* strains by immunoblot and bacteraemia study respectively, but **Blaser** did not teach or suggest any evaluation or measurement of immune response to *C. fetus* in a mammalian host.

The Examiner argued that **Lubitz** et al. did not teach away from the present invention and **Lubitz** was cited for what the reference taught with respect to S-layer being carrier proteins for heterologous antigens. Applicants strongly disagree.

Lubitz only taught the use of bacterial ghosts to carry immunogens by expressing a fusion protein that inserts into the bacterial membrane, not into the S-layer coat which is outside the outer membrane of the bacteria (column 2, lines 5-19, 56-58; Figure 2d). If the bacteria possess an additional S-layer coat, the S-layer is

also a component of the bacteria ghost, but the S-layer coat with its lipopolysaccharide only serves to enhance the immune responses to the antigens (column 2, lines 23-31; column 3, lines 2-6). Therefore, **Lubitz** did not teach or suggest S-layer being carrier proteins for heterologous antigens, nor did **Lubitz** teach or suggest modification of the S-layer or the sap homologs in *C. fetus* as claimed herein. Thus, combining the teaching of **Blaser** that did not teach or suggest making S-layer chimera which is expressed on the surface with the teaching of **Lubitz** that did not teach or suggest modification involving the S-layer would not result in the present invention of making modified *C. fetus* expressing altered S-layer proteins on the surface of the bacteria.

In view of the above remarks, the combined teaching of the cited references do not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicants' claimed invention. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the rejection of claims 1-2, 4-9 under 35 U.S.C. §103(a) be withdrawn.

Claims 1-2, 4-8 were rejected under 35 U.S.C. §103(a) as being unpatentable over **Blaser** (1994) in view of **Szostak** et al (1996). The rejection is respectfully traversed.

The Examiner argued that "**Blaser** does administer the recombinant C. fetus strain to a host for the evaluation of challenge experiments" and "evaluated the immune response...". Applicants strongly disagree. As discussed above, **Blaser** only disclosed the antigenic and virulence characteristics of the mutant *C. fetus* strains by immunoblot and challenge experiments respectively, but **Blaser** did not teach or suggest any evaluation or measurement of immune response to *C. fetus* in a mammalian host.

The Examiner argued that page 193 of **Szostak** taught about recombinant S-layer. However, **Szostak** et al. (1996) does not contain page 193. Applicants submit that **Szostak** et al. (1996) is essentially the same as **Lubitz** et al. discussed above. **Szostak** taught the use of bacterial ghosts to carry immunogens by expressing a fusion protein that inserts into the bacterial membrane, specifically the inner membrane of the bacteria (see abstract, line 7). **Szostak** did not teach or suggest S-layer being carrier proteins

for heterologous antigens, nor did **Szostak** teach or suggest modification of the S-layer or the sap homologs in *C. fetus* as claimed herein. Thus, combining the teaching of **Blaser** that did not teach or suggest making S-layer chimera which is expressed on the surface with the teaching of **Szostak** that did not teach or suggest modification involving the S-layer would not result in the present invention of making modified *C. fetus* expressing altered S-layer proteins on the surface of the bacteria.

In view of the above remarks, the combined teaching of the cited references do not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicants' claimed invention. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the rejection of claims 1-2, 4-8 under 35 U.S.C. §103(a) be withdrawn.

New Ground Of Rejection

Claim 1 was rejected under 35 U.S.C. §112, first paragraph, for lack of possession of the claimed invention. The rejection is respectfully traversed.

The Examiner rejected the phrase "non-naturally occurring" in the amended claim filed in response to a 35 U.S.C. §101 rejection. The Examiner argued that the claim limitation was not supported in the specification. Applicants respectfully disagree. Naturally occurring *Campylobacter fetus* bacteria have 7-9 highly homologous gene cassettes encoding different *sapA* homologs. As it is readily understood by one of ordinary skill in the art, these *sapA* homologs are homologous, not heterologous, proteins with respect to the bacteria that expresses the proteins. In contrast, the mutant strain of the present invention contains DNA cassette that encodes a heterologous protein, i.e. a foreign protein with respect to the mutant strain, and the claimed *C. fetus* bacteria expressing a chimeric S-layer protein containing a heterologous foreign protein is non-naturally occurring. Disclosure of the non-naturally occurring *C. fetus* bacteria can be found in Examples 9 and 19.

Claim 1 has been amended to recite a genetically engineered *C. fetus* strain. As it is readily understood by one of ordinary skill in the art, genetic engineering and genetically engineered products clearly involve the hand of man. Applicants submit that claim 1 is drawn to a statutory subject matter, and it is fully supported in the specification. Accordingly, Applicants respectfully request that the rejection of claim 1 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claim 18 was rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The rejection is respectfully traversed.

Claim 18 has been amended to recite all but one of the seven to nine *sapA* homologs are altered in the mutant strains. Accordingly, Applicants respectfully request that the rejection of claim 18 under 35 U.S.C. §112, second paragraph, be withdrawn.

Allowable Subject Matter

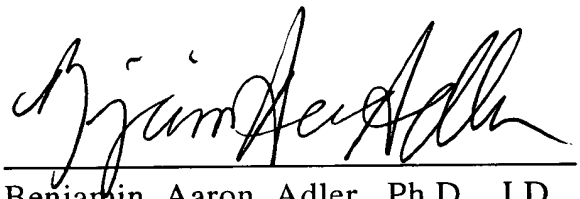
The Examiner stated that claim 15 defines allowable subject matter if it is rewritten in independent form including all of

the limitations of the base claim and a deposit of the genetic material contained therein. Applicants submit that claim 15 has been amended to recite all of the limitations of the base claim, and document showing deposit of the genetic material contained therein will be furnished to the Examiner as soon as the document is received by the Applicants.

This is intended to be a complete response to the Office Action mailed November 22, 2000. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: May 22, 2001



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 2, 4 and 14 have been cancelled.

Claim 1 has been amended as follows:

1. (twice amended) A ~~non-naturally occurring~~ genetically engineered mutant *C. fetus* strain useful for vaccinating an animal to *Campylobacter fetus*, wherein said strain is mutated to contain a DNA cassette encoding a heterologous protein, wherein the insertion of said DNA cassette results in alteration of a *sapA* homolog, and the expression of said DNA cassette results in surface expression of a S-layer protein that represents a chimera between the native S-layer protein and the heterologous protein encoded by said DNA cassette.

Claim 15 has been amended as follows:

15. (amended) ~~The strain of claim 14, wherein said bacterium is~~ A strain of *Escherichia coli.* modified to express *SapCDEF* genes.

Claim 16 has been amended as follows:

16. (amended) The ~~strain~~ *Escherichia coli*. of claim ~~14~~ 15, wherein a heterologous protein is expressed as a chimeric protein composed of sequences of heterologous origin, sequences that direct the secretion of said chimeric protein to the cell surface and sequences that direct the binding of the secreted chimeric protein to the lipopolysaccharides of the bacterial cell surface via the sapCDEF directed type 1 secretory system.

Claim 17 has been amended as follows:

17. (amended) A method of immunizing a host to generate immune responses to an immunogen, comprising the step of administering to said host a pharmacologically effective dose of the *Escherichia coli*. ~~strain~~ of claim ~~14~~ 15.

Claim 18 has been amended as follows:

18. (amended) The mutant *C. fetus* strain of claim 1, wherein all but one of the seven to nine *sapA* homologs are altered due to the insertion of said DNA cassette.